1. Sukhatme, USPN 5,869,230, filed 03/30/1995, of record, described a method of infecting an organ or a tissue other than a liver with an effective amount of a vector carrying g netic material of interest. While this method, which is patentably distinct from that of applicants, succeeded in transferring the genetic material into the kidney, the only cells affected were the endothelial cells of the inner and outer medulla; no gene transfer occurred into renal glomerular cells.

2. Tryggvason *et al*, USPN 6,342,214, filed 03/23/1998 (new IDS), also described a method for delivery of viral vector gene therapy pharmaceuticals to organs, including the kidney, but this technique involved the use of a recirculating, oxygenated perfusate solution at 37°C, rather than the single pass at room temperature used in the present invention.

3. Kitamura, USPN 5,580,558, filed 11/17/1993 (new IDS), Zhu *et al. Gene Therapy* 3:298 (1996), of record, Kitamura *et al., J Clin Invest* 94:497 (1994) (new IDS); Kitamura *et al. PNAS* 93:7387 (1996) (new IDS) all described methods that achieve site-directed delivery of exogenous gene product within renal glomeruli by first intoducing a gene-carrying vector into mesangial cells, and then infusing the cells into the kidney through the renal artery, where they were entrapped by glomeruli.

Comment on references 1-3:

Applicants note that the level of support for §101 usefulness of the claimed method in the aforelisted contemporaneous patents is no greater than that supplied by the present applicants, and is, in fact, less.

4. Heikkila *et al. Gene Therapy* 3:21 (1996), of record, attempted, but failed, to achieve viral vector-gen transfer into any kidney cells when the genetic

material was injected directly into the renal artery. They succeeded in transferring the gen into kidney cells only by continuous perfusion for 12 hrs.

5. Moullier *et al. Kidney Int.* 45:1220 (1994), of record, also perfused a gene-viral vector into the renal artery of rats or injected the gene vector into the renal artery, but the gene appeared only in tubular cells, not glomeruli.

6. Zhu *et al, Kidney Int.* 52:992 (1997) (new IDS) attempted to target a gene vector into kidney glomeruli, but did not succeed directly. Rather, the gene vector was given paranterally to the test animal, whereupon the gene concentrated in hepatocytes intensely. Hepatocytes, released from the liver into the general circulation, traveled to the kidneys, whereupon the gene incorporated into glomeruli. In the present invention, steps were taken to ensure that gene, injected into the renal artery, did not escape into the general circulation.

7. Lipkowitz *et al Am. J. Kidney Dis.* 28:475 (1996); *J Am Soc Nephrology* 10:1908 (1999) (both in new IDS) reviews molecular therapy for kidney diseases, and refers in the Abstract to significant barriers before successful organ-specific molecular therapy can be applied to the kidney., such as the need for kidney specificity. In the Summary, the authors also refer to the need to refine viral delivery systems so that there are high level transductions into specific renal cell types *e.g.*, glomeruli.

8. Kelley *et al., Am J Physiol* 276: F-1 (1999) (new IDS) is a review article on gene transfer in the kidney, discussing the various approaches used to date, including those shown above in paragraphs 1-7. As noted in the Conclusions, the authors state that constructing data bases for vectors and gene transfer methods for the normal and diseased kidney are critical first steps in the treatment of kidney diseases in patients.

9. Tomita *et al BBRC* 186: 129 (1992), Akami *et al, Trans. Proc.* 26:1315(1994) and Imai *et al Expert Opin Invest. Drugs* 10: (2000) (all in new IDS) stressed that the developm nt of methods for gene transfer into kidney cells is critical for future gene therapeutics. In this paper, they describe the administration to the renal artery of liposome-encapsulated gene-viral vectors, and detected the gene in glomeruli 4 days thereafter.

10. Chen *et al J Am Soc Nephrol* 14:947 (2003) (new IDS) describe gene delivery in renal tubular epithelial cells using adeno-associated viral vectors that avoid immunological barriers.

11. Kluth *et al Gene Therapy* 7:263(2000) (new IDS) used macrophage cells for *in vivo* delivery of genes to inflamed glomeruli of rats with inflammatory kidney disease.

These 16 state-of-the-art contemporaneous references, which constitute by no means an exhaustive list, show clearly that tranferring genes into specific kidney cells was an extremely active field and suggest strongly that those of average skills in this art would appreciate the present invention and recognize its credible, specific and substantial utility.

Batshaw Declaration of Expert Opinion

MPEP §2107 II(B)(1)(ii) states that credibility is assessed from the perspective of one who is ordinarily skilled in the art in view of the disclosure and any other evidence of record (test data, expert opinions, patent and printed publications).

The aforementioned test data for the claimed invention appears in the examples of the specification. It is clear that the data showed that the claimed

method was highly succ ssful in transferring gene-viral vector complexes into renal glomerular cells.

In Paper 11, the examiner dismissed Dr. Batshaw's expert opinion as being merely "opinion". Applicants argued at the Interview that opinions are precisely what one expects from an expert in a judicial or quasi-judicial proceeding. The Primary Examiner concurred, and stated that Dr. Batshaw's opinion must be considered. Dr. Batshaw referred to the present invention as being useful as an animal model that could logically be used to rank gene vectors for transfer into renal glomerular cells. The examiners suggested that references describing animal models for similar purposes would overcome this objection to the experts opinion.

As the examiners surely know, animal models for testing pharmaceuticals are hardly new. The pharmaceutical industry has used such models for decades. A few, particularly relevant literature references (listed in the new IDS), will illustrate this point.

1. In Ferrara, *J. Mol. Med.* 77:527 (1999), the gene technology company Genentech described animal models for determining the molecular and biological properties of Vascular Endothelial Growth Factor (VEGF). On p.536 there is a description of adenoviral-mediated gene transfer of VEGF121 being studied in a pig model. On p.537: gene therapy with the VEGF gene is used to promote endothelial cell growth in animal models.

2. In Culver Bone Marrow Transplant, suppl. 3:36 (1996), the company OncorPharm described animal models in which tumor cells, genetically altered with antisense IGF-1 or IL-2 genes, induced a potent, cell-mediated antitumor response. In addition, in animal models the multiple drug resistance (MDR-1) gene was transferred into stem cells to protect them from toxic chemotherapeutic

agents.

3. Wagner *et al Nephrol. Dial Trans* 10:1801 (1995) described renal gene transfer techniques in animal models to treat kidney disease.

4. Chen *et al J Am Soc Nephrol* 14:947 (2003) described the intrarenal delivery into renal tubular epithelial cells of an animal model of adeno-associated viral vectors carrying genes.

5. Merta *et al Sb Lek* 100:259 (1999) describe the principles and development of experimental animal models to first trials of gene therapeutics in polycystic kidney disease.

6. Stone *et al Prog Clin Biol Res* 229:73 (1987), in this state-of-the-art review article, refer to nonhuman primates as ideally suited as models in the "new area of gene therapy" in which genes will be transferred from one individual to another with a recessive gene.

7. Takeshita *et al BBRC* 227:628 (1996) from Genentech described therapeutic angiogenesis following arterial gene transfer of VEGF into a rabbit model of hind limb ischemia.

8. Herold *et al Kidney Int Suppl* 61:Suppl1:3 (2002) reported on the use of a herpes simplex vector as a model vector for studying gene involvement in renal disease relating to epithelial cells.

Applicants submit that these contemporaneous references support Dr. Batshaw's contention that animal models are in widespread use throughout the world in developing suitable therapies in gene-linked renal and other diseases.

CONCLUSION

The applicants, having established, using the Patent Office's own rules, that the present invention would be considered by those of ordinary skill in this art as having a credible, specific and substantial utility, respectfully request withdrawal of all §§ 101 and 101/112 rejections, and the passage of this application to allowance and issue.

Respectfully submitted,

Dr. Melvin Blecher
Attorney-at-Law
Reg. No. 33,649

Date: 08/19/2003

Law Offices of Dr. Melvin Blecher
4329 Van Ness St., NW
Washington, DC 20016-5625
Tel. 202 363 3338
Fax 202 362 8404

Clean Copy Of Claims

1. A method of] transferring into the glomerular cells of a kidney of a model mammal] a gene or genes of interest, comprising the step of infusing intra-renal arterially and continuously in a single pass through the superior mesenteric artery or renal artery an effective amount of a recombinant adenovirus vector carrying said gene or genes of interest into said kidney at an effectively slow rate over an effective period of time, under conditions such that at least 30% of said glomerular cells are infected with said vector, wherein said adenovirus vector carries a control element that allows expression of said gene or genes of interest in renal glomerular cells.

2. The method according to claim 1, wherein said control element comprises a cytomegalovirus enhancer and a chicken beta-actin promoter.

3. The method according to claim 1, wherein said kidney is maintained at reduced temperatures during said infusion procedure,

4. The method according to claim 1, further comprising clamping the aorta above and below said superior mesenteric renal artery of said kidney, and infusing through said superior mesenteric renal artery.

5. The method of claim 1, wherein said renal artery is cannulated directly without clamping of said aorta during said infusion.

6. The method of claim 1, wherein said mammal is a rodent, said rate of infusion is about 0.1- 0.5 x 10^{11} particles per minute, and said effective period of adenoviral vector infusion is between about 15 and 120 minutes.

7. The method according to claim 1, further comprising concurrent cannulation of the femoral vein through the vena cava into the renal vein so as to

direct vector not taken up by renal glomerular cells away from the general circulation.

8. The method according to claim 1, wherein said gene is the lacZ gene.

9. The method according to claim 1, wherein said gene encodes a growth factor.

10. The method according to claim 9, wherein said growth factor is selected from the group consisting of fibroblast growth factor, vascular endothelial growth factor, transforming growth factor beta, platelet-derived growth factor, and granulocyte-macrophage colony-stimulating growth factor.

11. The method according to claim 1, wherein said gene encodes a chemikine.

12. The method according to claim 11, wherein said chemikine is selected from the group consisting of monocyte chemoattractant protein-1, macrophage inflammatory protein-1 and -2, and cytokine induced neutrophil chemoattractants.

13. The method according to claim 1, wherein said gene encodes Green Fluorescence Protein.

14. The method according to claim 1, wherein said gene encodes Erythropoetin.

15. The method according to claim 1, wherein said gene encodes CD-2-AssociatedProtein.

16. The method according to claim 1, wherein said gene encodes Nephrin.